DETAILED ACTION

Response to Arguments

This Office Action is in response to the amendment submitted on 07/24/09. Claims 1-10 are currently pending in the application, with claims 8-10 having being withdrawn. Accordingly, claims 1-7 are being examined on the merits herein.

Receipt of the aforementioned amended claims is acknowledged and has been entered.

Applicant's arguments with respect to the rejection of claims 1-7 under 35 U.S.C. § 112, first paragraph has been fully considered. Given that applicant has deleted the term "prevention", such rejection is now moot. Consequently, the rejection of claims 1-7 under 35 U.S.C. § 112, first paragraph is hereby withdrawn.

Applicant's argument with respect to the rejection of claims 1 and 3-7 over Kobori has been fully considered. Applicant argues that autoimmune arthritis is a disease different from other anti-inflammatory diseases. Applicant further argues that rheumatoid arthritis (RA) is such a disease whose mechanism operates through the immune system and that Kobori is insufficient to provide an expectation of success that would lead one of ordinary skill in the art to the claimed invention. Such arguments are not persuasive as applicant is arguing the amended claims. It is noted that the features upon which applicant relies (i.e., autoimmune arthritis and effective amount of

coumestans) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). As a result, such arguments are moot.

Moreover, the Examiner contends that Kobori et al. did in fact render obvious applicant's invention since Kobori teaches the use of wedelolactone (i.e. applicant's elected species) for anti-inflammatory effects. Additionally, Kobori demonstrated that wedelolactone was effective in inhibiting IKK activity thereby affecting the NF_kB pathway and effective in inhibiting the secretion of the pro-inflammatory cytokine IL-1ß. Importantly, Kobori discloses that because of the ability of wedelolactone to inhibit the activation of NF_kB pathway, wedelolactone provides an interesting lead compound in anti-inflammatory therapy in diseases such as RA.

While Kobori did not teach RA as an autoimmune disease, the Examiner refers applicant to Lau who teaches that RA is an autoimmune disease (see abstract). Specifically, Lau teaches that the immune system is responsible for manifestations which include destruction of infecting organisms and the autoimmune reaction which is thought to be a malfunction of the system (see col.1, lines 28-31). It is now recognized that for various reasons and in view of various factors, the mammalian body may produce antibodies against parts of itself resulting in autoimmune diseases which include RA (see col. 1, lines 31-37; col. 2, lines 43-52; and col. 3, lines 1-13). Consequently, the Examiner maintains that because RA is an autoimmune disease, the teachings of Kobori still read on the limitations of the claims. As a result, the Examiner

maintains that in light of the teachings of Kobori, one of ordinary skill in the art would have indeed found it obvious to try wedelolactone in the treatment of autoimmune arthritis, particularly RA, since Kobori teaches that wedelolactone has anti-inflammatory effects and since Kobori proposes the use of wedelolactone for the treatment of RA and RA is characterized by inflammation. Similarly, one of ordinary skill in the art would have found it obvious to utilize and obvious to try wedelolactone for treating the autoimmune disease RA given that Kobori demonstrated that wedelolactone was effective in inhibiting NF_kB via inhibition of IKK and caspase 11 and NF_kB was taught as a pathway involved in pro-inflammatory stimuli (see Kobori, pg. 128, right col.). The examiner therefore contends that one of ordinary skill at the time of the invention would have had a reasonable expectation of success since NF_kB is a pro-inflammatory pathway, RA is characterized by inflammation, and given that Kobori demonstrated inhibition of NF_kB. For the foregoing reasons

As for applicant's arguments that Kobori simply presents guesswork that inhibition of IL-1ß is desired for treating RA since Matsui reports that IL-18 plays an important role in RA, such arguments are not persuasive since Matsui was not utilized in the obvious rejection over Kobori. However, even if arguendo Matsui was used in the aforementioned rejection, the Examiner directs applicant's attention where Matsui clearly teaches that IL-18 activates NF_kB, the same pathway purported by Kobori to be involved in RA (see pg. 703, fig. 2). Moreover, Matsui further teaches that RA patients not only possess IL-18 positive cells, but also IL-1 (i.e. a cytokine) or TNF-α (i.e. cytokine) positive cells in their RA synovia (see pg. 709, right col., paragraph 2 and pg.

710, figure 5) thereby supporting the notion that other inflammatory cytokines are involved in RA and the fact that Matsui chooses to focus on a particular cytokine does not negate the fact that IL-1ß is also involved in RA. In fact, Matsui teaches that IL-18 induces inflammatory factors involved in the development of RA including TNF-α and IL-1ß (see pg. 712, right col., paragraph 2). As a result, the Examiner contends that in light of the prior art who teaches that IL-1ß is an inflammatory cytokine involved in RA, that NF_kB is a pathway involved in RA, and Kobori who demonstrated that wedelolactone was effective in inhibiting activation of the NF_kB pathway and who further suggest the use of wedelolactone in RA, one of ordinary skill in the art at the time of the invention would have indeed found it obvious to utilize and obvious to try wedelolactone in the treatment of RA and with a reasonable expectation of success since Kobori demonstrated inhibition of NF_kB, the same pathway activated in RA disease. As a result, the Examiner maintains that Kobori does indeed render obvious applicant's invention.

As for Applicant's arguments that 1) a compound can inhibit one pathway but does not mean such compound is effective in treating immune inflammation; 2) commonly known compounds that are effective in treating common inflammation have not translated to effective treatment of immune inflammation; and 3) that no animal experimental data was provided to predict whether a compound is effective in treating immune inflammation such as RA, such arguments are not found persuasive as they are mere conclusionary statements. The MPEP clearly states that under the obvious to

try rationale, if the Graham factual inquiries are resolved along with demonstration of need in the art, finite number of solutions, and reasonable expectation of success, the claims can be rendered obvious. In this instance, the prior art did in fact establish a *prima facie* case of obviousness. For the foregoing reasons, the Examiner contends that Yuan in view of Matsui and Kobori do indeed render obvious applicant's invention.

For the foregoing reasons, the rejection under 35 U.S.C. § 112, first paragraph is hereby withdrawn but the 103(a) rejections remain proper. However, in view of applicant's amendment, the following modified 103 (a) Final rejections are being made.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 3-7 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Kobori et al. (Cell Death and Differentiation, Oct. 3, 2003, published online, Vol. 11, pgs. 123-130; previously cited) in view of Lau (U.S. 4,705,687).

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Kobori et al. teach that wedelolactone (i.e. applicant's elected species) has been identified as a coumestan contained in E. prostrate L. and was suggested to be the active component of this herb (see pg. 128, left col., Discussion and pg. 124, left col. paragraph 2). Kobori et al. also demonstrated that wedelolactone has anti-inflammatory effect through inhibition of IKK activity and caspase-11 expression (see pg. 128, left col. and right col. line 1). In fact, Kobori et al. teach that wedelolactone was able to inhibit the secretion of pro-inflammatory cytokine IL-1ß, which is maturated by caspase-11 activated caspase 1 (see pg. 128, right col., lines 1-3). Moreover, Kobori et al. teach that due to the ability of wedelolactone to inhibit the activation of NF-kB pathway, such compound provides an interesting potential lead compound in anti-inflammatory therapy in diseases such as rheumatoid arthritis (see pg. 128, right col., paragraph 2). Additionally, Kobori et al. teach that isolating wedelolactone from E. prostrate L. wherein the dried entire plants were homogenized in ethanol with a blender (see pg. 129, left

col., paragraph 3). The ethanol extract is then filtered and the supernatant of the filtrate is then concentrated by evaporation and then washed with hot water (see pg. 129, left col., paragraph 3). The hot water fraction was partitioned with ethyl acetate and the ethylacetate fraction was concentrated by evaporation. The dried ethylacetate fraction was dissolved in ethanol and further fractionated to result in a precipitate. The precipitate was then washed several times, dissolved in a small amount of DMSO and recrystallized in ethanol. The precipitate and the wedelolactone were separated and identified by UV spectrum, MS spectra (see pg. 129, left col., Isolation of wedelolactone from *E. prostrata L).*

Kobori et al. do not specifically teach that the method of obtaining the aforementioned compound (i.e. wedelolactone) involves eluting the precipitate on a silica gel column with gradients of petroleum ether/acetone mixture or dichloromethane/acetone mixture or a toluene/acetone/formate mixture. Similarly, Kobori et al. do not teach a method of treating autoimmune arthritis.

Kobori et al. however do teach that wedelolactone which comes from the extract of *E. prostrata L.* is a potential compound in the treatment of anti-inflammatory diseases including rheumatoid arthritis. Moreover, Kobori et al. teach that the aforementioned compound can be extracted from the entire plant, filtered, concentrated, and washed with hot water which necessarily reads on applicant's claim limitation of water temperature of 50-80 °C. While Kobori et al. is silent on elution of the precipitate using

petroleum ether/acetone mixture, dichloromethane/acetone mixture, or a toluene-acetone-formate mixture, it is the Examiner's contention that the resulting precipitate of the prior art is substantially the same as that of applicant regardless of the type of elution solvents utilized. Consequently, a *prima facie* case of obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977).

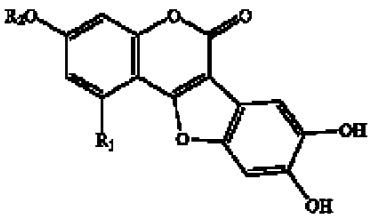
Lau teaches that RA is an autoimmune disease (see abstract). Specifically, Lau teaches that the immune system is responsible for manifestations which include destruction of infecting organisms and the autoimmune reaction which is thought to be a malfunction of the system (see col.1, lines 28-31). It is now recognized that for various reasons and in view of various factors, the mammalian body may produce antibodies against parts of itself resulting in autoimmune diseases which include RA (see col. 1, lines 31-37; col. 2, lines 43-52; and col. 3, lines 1-13). Consequently, the Examiner maintains that because Lau teaches that RA is an autoimmune disease, RA is considered as an autoimmune type of arthritis.

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize and obvious to try the wedelolactone compound of Kobori et al. to treat the autoimmune disease rheumatoid arthritis since Kobori et al. teach that wedelolactone is a potential compound in the treatment of anti-inflammatory disease including rheumatoid arthritis and in view of Lau who teaches that RA is an autoimmune disease. Given the teachings of Kobori and Lau, one of ordinary skill would have been

motivated to utilize and motivated to try the compound of Kobori et al. to treat rheumatoid arthritis as taught by Kobori et al. with the reasonable expectation of providing a method that is efficient in treating rheumatoid arthritis and other inflammatory diseases.

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yuan et al. (U.S. 6,552,071 B2, previously cited) in view of Lau (U.S. 4,705,687) and in further view of Matsui et al. (Exp. Opin. Theur. Targets, 2003, Vol. 7, No. 6, pgs. 701-724, previously cited).

Yuan et al. teach methods and compounds for treating inflammation (see abstract and col. 1, lines 13-15). The methods involve the use of the plant extract wedelolactone or comprise administering wedelolactone or a salt thereof to a subject (see col. 1, lines 43-46 and 55-62). Particularly, Yuan et al. teach a method of treating inflammation in a subject involving administering in a pharmaceutically acceptable carrier a compound having the formula:



where R1 is OH and R2 is CH3 (see col. 2, lines 18-36 and 59-64). Yuan et al. further teach that by plant extract, it is meant that a compound of mixture of compounds that are obtained from a plant may be used after obtaining such mixture by chopping the

entire plant into small pieces, treating the plant with high pressure, distilling the plant or treating the plant with solvent and further teach the use of *Eclipta prostrate L.* extract as responsible for inhibiting pro-inflammatory cytokines such as caspase-11 and which contains wedelolactone (see col. 4, lines 24-29, 55-58 and example 3). Yuan et al. further teach extraction of Eclipta prostrate L. with ethanol followed by concentration through evaporation (see col. 11-12, example 2). The dried ethanol extract was next washed with boiling water which necessarily reads on applicant's claim limitation of a boiling temperature of 50-80 °C since such temperature render obvious the fact that the water would be boiling. The boiling water was then partitioned with ethyl acetate and the ethyl acetate fraction which contains the active ingredient (i.e. wedelolactone) was further purified by silica gel chromatography and preparative high pressure liquid chromatography (HPLC) and components identified using thin layer chromatography (see col. 12-13, example 4). Yuan et al. importantly teach that the ethanol extract fraction and the boiling water extract both contain wedelolactone which suppress the expression of caspase-11 (see col. 13, lines 22-23).

Yuan et al. do not specifically teach that the method of obtaining the aforementioned compound (i.e. wedelolactone) involves eluting the precipitate on a silica gel column with gradients of petroleum ether/acetone mixture or dichloromethane/acetone mixture or a toluene/acetone/formate mixture. Similarly, Yuan et al. do not teach a method of treating autoimmune arthritis.

Yuan et al. however do teach that wedelolactone which comes from the extract of *E. prostrata L.* is a potential compound in the treatment of anti-inflammatory diseases including rheumatoid arthritis. Moreover, Yuan et al. teach that the aforementioned compound can be extracted from the entire plant, chopped into pieces, concentrated, and washed with boiling water which necessarily reads on applicant's claim limitation of water temperature of 50-80 °C. While Yuan et al. is silent on elution of the precipitate using petroleum ether/acetone mixture, dichloromethane/acetone mixture, or a toluene-acetone-formate mixture, it is the Examiner's contention that the resulting precipitate of the prior art is substantially the same as that of applicant regardless of the type of elution solvents utilized. Consequently, a *prima facie* case of obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). Moreover, given that Yuan et al. teach the salts of wedelolactone, the Examiner contends that such term render obvious applicant's disclosed salts in claim 2.

Lau teaches that RA is an autoimmune disease (see abstract). Specifically, Lau teaches that the immune system is responsible for manifestations which include destruction of infecting organisms and the autoimmune reaction which is thought to be a malfunction of the system (see col.1, lines 28-31). It is now recognized that for various reasons and in view of various factors, the mammalian body may produce antibodies against parts of itself resulting in autoimmune diseases which include RA (see col. 1, lines 31-37; col. 2, lines 43-52; and col. 3, lines 1-13). Consequently, the Examiner

maintains that because Lau teaches that RA is an autoimmune disease, RA is considered as an autoimmune type of arthritis.

Matsui et al. teach that Rheumatoid arthritis (RA) is a common chronic inflammatory joint disease with destruction of the cartilage and bone (see pg. 708, left col.). RA is characterized by the intensively proliferating synoviocytes and the dense infiltration of various types of activated immune competent cells (i.e. suggestive of an immune based disease; see pg. 708, left col.). Matsui et al. further teach that RA patients possess aberrant T cells which react with collagen type II autoantigens which have been found to induce inflammatory arthritis in mice (see pg. 709, left col., paragraph 1). Importantly, Matsui et al. teach that cytokines and chemokines are involved in the development of RA and that RA patients tend to show an increase in pro-inflammatory cytokines including IL-1, TNF-α, and IL-6 (see pg. 709, left col., paragraph 2).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize and obvious to try the wedelolactone compound or plant extract of wedelolactone of Yuan et al. to treat the autoimmune disease rheumatoid arthritis since Yuan et al. teach that wedelolactone is effective against inflammation, and Lau teaches that RA is a type of autoimmune disease, and Matsui et al. teach that Rheumatoid arthritis is an inflammatory disease characterized by infiltration of inflammatory cytokines. Given the teachings of Yuan, Lau, and Matsui, one of ordinary

skill would have been motivated to utilize and motivated to try the compound or extract of Yuan et al. to treat rheumatoid arthritis as taught by Matsui and Lau with the reasonable expectation of providing a method that is efficient in treating rheumatoid arthritis and other inflammatory diseases.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samira Jean-Louis whose telephone number is 571-270-3503. The examiner can normally be reached on 7:30-6 PM EST M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. J. L. /

Examiner, Art Unit 1627

10/21/2009

/Shengjun Wang/

Primary Examiner, Art Unit 1627